RIAMET 20 mg/120 mg, tablet
B/24 tablets (CIP: 34009 276 033 0 3)

Applicant: NOVARTIS PHARMA S.A.S.

<table>
<thead>
<tr>
<th>INN</th>
<th>artemether, lumefantrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC Code (2012):</td>
<td>P01BF01 (antimalarials: artemisinin and derivatives, combinations)</td>
</tr>
<tr>
<td>Reason for the review</td>
<td>Inclusion</td>
</tr>
<tr>
<td>Lists concerned</td>
<td>National Health Insurance (French Social Security Code L.162-17)</td>
</tr>
<tr>
<td></td>
<td>Hospital use (French Public Health Code L.5123 2)</td>
</tr>
<tr>
<td>Indication concerned</td>
<td>&quot;Treatment of uncomplicated <em>Plasmodium falciparum</em> malaria in adults, children and infants of 5 kg and above.&quot;</td>
</tr>
<tr>
<td><strong>AB</strong></td>
<td>The actual benefit of RIAMET in the treatment of uncomplicated <em>Plasmodium falciparum</em> malaria is substantial.</td>
</tr>
<tr>
<td><strong>IAB</strong></td>
<td>Given its efficacy in the treatment of uncomplicated malaria, particularly in the case of multidrug-resistant strains, and a lower risk of developing resistance with combinations containing artemisinin derivatives compared with traditional monotherapies, particularly in children and in malaria-endemic areas (mainly French Guiana and Mayotte), the proprietary medicinal product RIAMET, like the proprietary medicinal product EURARTESIM, provides a minor improvement in actual benefit (IAB IV) in the treatment of uncomplicated <em>Plasmodium falciparum</em> malaria.</td>
</tr>
</tbody>
</table>
01 **ADMINISTRATIVE AND REGULATORY INFORMATION**

| Marketing Authorisation (European) | Initial: 23 April 2001 (mutual recognition)  
Revision: 31 December 2013 (reference to "medicine for hospital prescription" deleted) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribing and dispensing conditions/special status</td>
<td>List I</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATC Classification</th>
<th>2012</th>
<th>P</th>
<th>Antiparasitic products, insecticides and repellants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P01</td>
<td></td>
<td>Antiprotozoals</td>
</tr>
<tr>
<td></td>
<td>P01B</td>
<td></td>
<td>Antimalarials</td>
</tr>
<tr>
<td></td>
<td>P01BF</td>
<td></td>
<td>Artemisinin and derivatives, combinations</td>
</tr>
<tr>
<td></td>
<td>P01BF01</td>
<td></td>
<td>artemether and lumefantrine</td>
</tr>
</tbody>
</table>

02 **BACKGROUND**

Review of the application for inclusion of RIAMET 20 mg/120 mg, tablet on the list of medicines refundable by National Health Insurance, following the amendment to the prescribing conditions (reference to "medicine for hospital prescription" deleted).

The same presentation which currently has approval for hospital use only with the CIP code (34009 563 043 8 7) will be replaced with that of this opinion and given a new CIP code (34009 276 033 0 3).

At the time of its last opinion relating to the inclusion of RIAMET on the list of medicines approved for hospital use (in 2007), following a referral to the DGS [Directorate-General for Health] given the need expressed by healthcare professionals in French Guiana and Mayotte, the Committee issued a ruling on the AB of this proprietary medicinal product in adults but not on the IAB.

Moreover, within the context of the application for extension of indication to the paediatric population (in 2008), the Committee has granted RIAMET a minor IAB (level IV) in children.

03 **THERAPEUTIC INDICATION**

"Treatment of uncomplicated *Plasmodium falciparum* malaria in adults, children and infants of 5 kg and above.

Consideration should be given to current recommendations regarding the appropriate use of antimalarials."

04 **DOSAGE**

"**Adults and children aged 12 years or over weighing 35 kg or above:**

The total course of treatment will be administered in six doses of four tablets (i.e. 24 tablets) given over a period of 60 hours according to the following regimen:

First dose, given at the time of initial diagnosis: four tablets.

Then five doses of four tablets given at 8, 24, 36, 48 and 60 hours thereafter.

**Children and infants weighing 5 kg to less than 35 kg:**

A six-dose regimen is recommended with 1 to 3 tablets per dose, depending on bodyweight:

- 5 to less than 15 kg bodyweight:
  - First dose, given at the time of initial diagnosis: One tablet.
Then five doses of one tablet given at 8, 24, 36, 48 and 60 hours thereafter.

15 to less than 25 kg bodyweight:
First dose, given at the time of initial diagnosis: two tablets.
Then five doses of two tablets given at 8, 24, 36, 48 and 60 thereafter.

25 to less than 35 kg bodyweight:
First dose, given at the time of initial diagnosis: three tablets.
Then five doses of three tablets given at 8, 24, 36, 48 and 60 hours thereafter.

05 THERAPEUTIC NEED

Delayed or inappropriate treatment of uncomplicated *P. falciparum* malaria may result in the disease evolving into a severe form which may be life-threatening for the patient. The curative treatment of malaria depends on the clinical form of the disease, the area, whether or not it is possible to administer an oral treatment, the *Plasmodiophora* species involved and the foreseeable existence of drug resistance.

According to the WHO, the provision of treatment combinations containing a derivative of artemisinin is essential and is a recognised response to the need to counter the risk that *P. falciparum* will become resistant to monotherapies, and to the spread of multidrug-resistance to traditional antimalarials. In France, the only combinations containing a derivative of artemisinin and with a Marketing Authorisation are the artemether + lumefantrine (RIAMET) and dihydroartemisinin + piperaquine (EURARTESIM) combinations.

In French Guiana and Mayotte, the only overseas departments and regions where malaria is endemic, the treatment is increasingly based on combinations of antimalarials with different mechanisms of action, taking into account the spread of multidrug resistance to traditional antimalarials and the risk of resistance to substances used in monotherapy. In this geographical area, the routine use of proprietary medicinal products RIAMET and EURARTESIM is a satisfactory alternative to the atovaquone-proguanil (MALARONE) combination. In metropolitan France (non-endemic area) where the multidrug resistant strains are rarer among the cases of imported malaria and where the risk of selection does not arise in the absence of transmission, these dual therapies are a useful alternative to the atovaquone-proguanil combination (MALARONE) and to mefloquine (LARIAM), especially given the poor tolerance sometimes observed with these treatments.

Given these points:
- In French Guiana and Mayotte (malaria-endemic areas), the artemether + lumefantrine (RIAMET) and dihydroartemisinin + piperaquine (EURARTESIM) combinations are the main curative treatments for uncomplicated *P. falciparum* malaria.
- In metropolitan France, the atovaquone + proguanil (MALARONE), artemether + lumefantrine (RIAMET) and dihydroartemisinin + piperaquine (EURARTESIM) combinations, as well as mefloquine (LARIAM) are the main curative treatments for uncomplicated *P. falciparum* malaria.

Currently, none of these reference drugs are refundable as pharmacy only medicines for the curative treatment of uncomplicated *P. falciparum* malaria. Only the proprietary medicinal products MALARONE and LARIAM are refundable as pharmacy only medicines for malaria prophylaxis by National Health Insurance in French Guiana. In addition, their inclusion on the list of medicines refundable by the whole National Health Insurance system could facilitate access to treatment for the patients able to be cared for in outpatients and thus avoid hospitalisations.

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06 CLINICALLY RELEVANT COMPARATORS

The clinically relevant comparators of RIAMET are first line curative treatments for uncomplicated *P. falciparum* malaria according to recommendations from the WHO1,2 and the SPILF [The French Speaking Infectious Disease Society],3 and they are available in France:

<table>
<thead>
<tr>
<th>NAME (INN)</th>
<th>Date of TC opinion (Reason for the review)</th>
<th>AB</th>
<th>IAB</th>
<th>Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>EURARTESIM (dihydroartemisinin + piperaquin) Sigma-Tau France</td>
<td>29/02/2012 (Inclusion)</td>
<td>Substantial</td>
<td>IAB V compared with RIAMET</td>
<td>Hospital use</td>
</tr>
<tr>
<td>LARIAM (mefloquine) Roche</td>
<td>19/03/2008 (re-assessment*)</td>
<td>Substantial</td>
<td>-</td>
<td>Hospital use</td>
</tr>
<tr>
<td>MALARONE and generics (atovaquone + proguanil) GlaxoSmithKline</td>
<td>19/03/2008 (re-assessment*) 18/02/2009 (indication extension for the paediatric population)</td>
<td>Substantial</td>
<td>IAB V in therapeutic use</td>
<td>Hospital use</td>
</tr>
</tbody>
</table>

* Re-assessment at the request of the DGS [Directorate-General for Health] in the prophylactic treatment of malaria for French Guiana and Mayotte National Health Insurance.

07 SUMMARY OF PREVIOUS ASSESSMENTS

In its previous opinions, the conclusions of the Committee were as follows:

<table>
<thead>
<tr>
<th>Date of opinion</th>
<th>2 October 2002 and 20 November 2002 (Inclusion for hospital use in adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB</td>
<td>&quot;The condition related to this proprietary medicinal product can be life-threatening. This proprietary medicinal product is intended as curative therapy. The efficacy/adverse effects ratio of this medicinal product cannot be evaluated in the current state of the documentation. This medicinal product is a first-line therapy. There are treatment alternatives.&quot;</td>
</tr>
<tr>
<td>IAB</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Transparency Committee recommendations</td>
<td>&quot;In order to provide additional data on the cardiotoxicity of the product, the following was requested whilst Riamet was being registered: - an in vitro cardiotoxicity study; a study on the HEK293 cells expressing HERG channels was provided. - a phase IV study comprising electrocardiographic monitoring; an intermediate analysis had to be submitted in December 2001. - the determination of pharmacokinetic parameters, particularly for the desbutyl-lumefantrine doses, active metabolite of lumefantrine. No result was submitted by the Marketing Authorisation holder relating to these last two points. The Committee considers itself unable to give an opinion on the application for inclusion on the list of medicines approved for use by hospitals and various public service&quot;.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date of opinion</th>
<th>14 March 2007 (Re-assessment following a referral to the DGS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB</td>
<td>&quot;Malaria is a serious disease on account of its potential deadliness when <em>Plasmodium falciparum</em> is involved. Strains of <em>Plasmodium falciparum</em> that are resistant to traditional treatments are becoming increasingly common. This parasitic disease is now covered by a WHO monitoring programme1. Dual therapy with artemether and lumefantrine (RIAMET) is intended as curative treatment. Its efficacy is satisfactory both in terms of the multidrug-resistant strains of <em>P. falciparum</em> of South East Asia and in terms of the moderately drug-resistant Sub-Saharan African strains, despite a dosage restricted to two doses a day over three days and a low bioavailability for lumefantrine (enhanced by the simultaneous intake of foods with lipids). RIAMET carries a risk of neurotoxicity associated with artemether and cardiotoxicity associated with lumefantrine. Despite this risk and after consultation with the AFSSAPS [French Healthcare Product Safety Agency], it does however appear that its safety profile is acceptable so long as the contraindications (including congenital QTc-interval prolongation and certain heart disease antecedents), warnings and precautions for use are observed. The proprietary medicinal product RIAMET is the only combination containing a derivative of artemisinin which has a European Marketing Authorisation. This is a satisfactory alternative to atovaquone-proguanil. Based on the current state of knowledge on the benefit of fixed-dose combination antimalarials containing a derivative of artemisinin, the actual benefit of the proprietary medicinal product RIAMET is substantial&quot;.</td>
</tr>
<tr>
<td>IAB</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
Malaria is a serious disease on account of its potential deadliness when *Plasmodium falciparum* is involved. Strains of *Plasmodium falciparum* that are resistant to traditional treatments are becoming increasingly common. This parasitic disease is now covered by a WHO monitoring programme.

Dual therapy with artemether and lumefantrine (RIAMET) is intended as curative treatment. The efficacy/adverse effects ratio is high so long as the contraindications (including congenital QTc-interval prolongation and certain heart disease antecedents), warnings and precautions for use are observed. The proprietary medicinal product RIAMET is the only dual therapy containing a derivative of artemisinin which has a European Marketing Authorisation. There are treatment alternatives.

**Public health benefit**

Uncomplicated *Plasmodium falciparum* malaria in children and infants of 5 kg and over represents a low public health burden in France. The fight against malaria, which requires an integrated approach that comprises prevention and treatment with effective antimalarials, is not considered to be a public health priority established at national level. However, in French Guiana and Mayotte, where malaria is endemic, having access to artemisinin-based treatment combinations does constitute a response recognised by the WHO to the need to counter the risk that *P. falciparum* will become resistant to monotherapies, and to the spread of multidrug resistance to traditional antimalarials. Given the available data, a theoretical impact is expected on the reduction of morbidity and mortality linked to uncomplicated *Plasmodium falciparum* malaria. Given the small number of children potentially affected by treatment with the artemether-lumefantrine combination (RIAMET) in France, no impact on a population level is expected. Consequently, given the response which RIAMET could provide to the specific need for the affected populations in French Guiana and Mayotte, a minor public health benefit is expected for this proprietary medicinal product.

The actual benefit of the proprietary medicinal product RIAMET remains substantial.

"Given its efficacy in the treatment of uncomplicated malaria, particularly in the case of multidrug-resistant strains and based on the current state of knowledge on safety, the proprietary medicinal product RIAMET provides a minor improvement in actual benefit (IAB IV) in the treatment of uncomplicated *Plasmodium falciparum* malaria in children and infants of 5 kg and over".

<table>
<thead>
<tr>
<th>Date of opinion</th>
<th><strong>16 July 2008 (extension of indication for paediatric population)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AB</strong></td>
<td>Malaria is a serious disease on account of its potential deadliness when <em>Plasmodium falciparum</em> is involved. Strains of <em>Plasmodium falciparum</em> that are resistant to traditional treatments are becoming increasingly common. This parasitic disease is now covered by a WHO monitoring programme. Dual therapy with artemether and lumefantrine (RIAMET) is intended as curative treatment. The efficacy/adverse effects ratio is high so long as the contraindications (including congenital QTc-interval prolongation and certain heart disease antecedents), warnings and precautions for use are observed. The proprietary medicinal product RIAMET is the only dual therapy containing a derivative of artemisinin which has a European Marketing Authorisation. There are treatment alternatives.</td>
</tr>
<tr>
<td><strong>IAB</strong></td>
<td>&quot;Given its efficacy in the treatment of uncomplicated malaria, particularly in the case of multidrug-resistant strains and based on the current state of knowledge on safety, the proprietary medicinal product RIAMET provides a minor improvement in actual benefit (IAB IV) in the treatment of uncomplicated <em>Plasmodium falciparum</em> malaria in children and infants of 5 kg and over&quot;.</td>
</tr>
</tbody>
</table>
08 ANALYSIS OF NEW AVAILABLE DATA

08.1 Efficacy

8.1.1 Summary of data taken into consideration in the Transparency Committee’s previous opinion (opinion of 16 July 2008)

In its previous opinion dated 16 July 2008, the Committee examined the results of the two uncontrolled studies which evaluated the efficacy of the artemether + lumefantrine combination in the treatment of uncomplicated *P. falciparum* malaria:

- a study performed in children weighing 5 to 25 kg in malaria endemic areas for whom the parasitological cure rate after 28 days was 93.9 % in the ITT population and 96.7 % in the population defined as evaluable (PP).
- a study performed in non-immunised adults for whom the parasitological cure rate after 28 days was 74.1 % in the ITT population and 96 % in the population defined as evaluable (PP).

8.1.2 New data

As part of the application for inclusion of RIAMET on the list of medicines refundable by National Health Insurance, the new clinical efficacy data presented by the company are essentially:

- a literature review, including a Cochrane meta analysis\(^4\) (9 randomised clinical studies), a meta-analysis using a Bayesian approach\(^5\) (32 randomised clinical studies) and a paediatric population meta analysis\(^6\) (17 randomised clinical studies);
- a phase III study in children (study DM040011, unpublished): a non inferiority study whose aim was to compare the efficacy and safety of the artemimol + piperaquine (EURARTESIM) combination with that of the artemether + lumefantrine (RIAMET) combination in children with uncomplicated *P. falciparum* malaria;
- a phase III study in children (study 2303, unpublished): a non inferiority study whose aim was to evaluate the efficacy and safety of two galenic forms (tablet *versus* dispersible tablet) of the artemether + lumefantrine (RIAMET) combination in children with uncomplicated *P. falciparum* malaria.

Omari Meta-Analysis (2005):\(^4\)

This is a Cochrane meta-analysis which included nine randomised clinical studies in which the artemether + lumefantrine (RIAMET) combination at the standard dose administered in six doses was compared with the following treatments:

- artemunate + mefloquine
- artemunate + amodiaquine
- dihydroartemisinin + naphthoquine-trimethoprim
- chloroquine + sulphadoxine-pyrimethamine
- amodiaquine + sulphadoxine-pyrimethamine
- amodiaquine

The percentage of failure of the treatment after 28 days was lower with the artemether + lumefantrine (RIAMET) combination than with amodiaquine alone (270 patients in one study), the amodiaquine + sulphadoxine-pyrimethamine combination (507 patients in one


study), but equal to that of the chloroquine + sulphadoxine-pyrimethamine combination (201 patients in two studies). In comparison to the other combinations containing a derivative of artemisinin, the arteether + lumefantrine (RIAMET) combination was more effective than the artesunate + amodiaquine combination (668 patients in two studies), as effective as the dihydroartemisinin + naphthoquine-trimethoprim combination (89 patients in one study) and less effective than the artesunate + mefloquine combination (270 patients in four studies).

The authors conclude that the artesunate + lumefantrine (RIAMET) combination at the standard dose administered in six doses seemed more effective than the antimalarial treatments not containing any derivative of artemisinin. On the other hand, the artesunate + mefloquine combination seems least to be as effective, even superior, compared with the artesunate + lumefantrine (RIAMET) combination.

**Jansen Meta-Analysis (2007):**
This is a meta-analysis using a Bayesian approach, which included 32 randomised clinical studies in which a combination containing a derivative of artemisinin was compared with at least one other treatment. Apart from the artesunate + lumefantrine (RIAMET) combination, the different combinations containing a derivative of artemisinin recorded in this study were:
- artesunate + amodiaquine
- artesunate + chloroquine
- artesunate + mefloquine
- artesunate + sulphadoxine-pyrimethamine

The percentage of PCR-corrected clinical and parasitological cure rate after 28 days was 97.4% with the artemether + lumefantrine (RIAMET) combination, 96.9% with the artesunate + mefloquine combination, 88.5% with the artesunate + amodiaquine combination and 45.8% with the artesunate + chloroquine combination.

The authors conclude that the artesunate + lumefantrine (RIAMET) combination is more effective than combinations containing a derivative of artemisinin.

**Ashley Meta-Analysis (2008):**
This is a paediatric population meta-analysis, which included 17 randomised clinical studies in which a combination containing a derivative of artemisinin was administered for 3 days, under medical supervision, with a follow-up after 28 days and PCR genotyping. Apart from the artesunate + lumefantrine (RIAMET) combination, the different combinations containing a derivative of artemisinin recorded in this study were:
- artesunate + amodiaquine
- artesunate + sulphadoxine-pyrimethamine

The percentage of failure of the treatment after 28 days was 0.0 to 3.3% with the artesunate + sulphadoxine-pyrimethamine combination and 0.0 to 39.3% with the artesunate + amodiaquine combination.

The authors conclude that the efficacy of the artesunate + lumefantrine (RIAMET) combination is significant whilst noting that the analysis was performed on a small number of patients.

It should be noted that the clinical studies included in these three meta-analyses compare the artesunate + lumefantrine (RIAMET) combination with treatment alternatives that are not available in France.

**Study DM040011 (unpublished):**
This is a phase III non-inferiority study whose aim was to compare the efficacy and safety of the artenimol + piperaquine (EURARTESIM) combination with that of the artesunate + lumefantrine (RIAMET) combination in children with uncomplicated *P. falciparum* malaria.

The results of this study which led to the non-inferiority of EURARTESIM compared with RIAMET to be established had already been evaluated by the Committee in its opinion on EURARTESIM on 29 February 2012. The conclusions of the Committee were as follows:

"In the per protocol (PP) population, the PCR-corrected cure percentages after 28 days were 95.7% (910/951) in the artenimol/piperaquine group versus 95.7% (442/462) in the artesunate/lumefantrine group (p = 0.998). The lower limit of the unilateral confidence interval of
the difference between the two groups was -2.24%, which established the non-inferiority of the artenimol/piperazine combination compared with the artemether/lumefantrine combination (non inferiority margin defined as -5%). Analysis of the intention to treat population (mITT) gave similar results: 92.7% (952/1027) versus 94.8% (471/497), lower limit of the unilateral confidence interval of the difference = -4.59%.

08.2 Safety/adverse effects

SPC data:
The most common adverse events are: vomiting, abdominal pain, headaches, cough and anorexia. These events are usually temporary and most often of low severity.
The artemether + lumefantrine (RIAMET) combination may cause a QT-interval prolongation. However, this risk is limited in the strict compliance with the contraindications (including patients with congenital QTc interval prolongation and certain heart disease antecedents) as well as warnings and precautions for use in its Marketing Authorisation.
It should be noted that changes to the SPC have been made since the Committee's previous opinions (14 March 2007 and 16 July 2008). These changes mainly relate to the updating of the frequency of adverse effects, the addition of data on the QT/QTc interval prolongation and the addition of pharmacokinetic data.

Data from pharmacovigilance:
The applicant has submitted the six periodic safety update reports (PSURs) relating to RIAMET covering the period from 1 May 2007 to 31 October 2011.
The analysis of these data mainly showed three new cases of Stevens Johnson syndrome including two cases where RIAMET was combined with phenobarbital including one which led to the death of a patient.

08.3 Prescription data

According to data submitted by the company, RIAMET was prescribed about 1500 times a year, with 75% of prescriptions in the overseas departments and regions, limited almost exclusively to French Guiana and Mayotte.

08.4 Summary & discussion

These new data are not such as to alter the previous conclusions of the Committee (opinion of 14 March 2007 and 16 July 2008) on the efficacy and safety of RIAMET in the treatment of uncomplicated *P. falciparum* malaria and allow consideration of the use of this medicine in outpatients.
The scientific data acquired on malaria and its treatment methods have also been taken into account. The therapeutic use of RIAMET has not altered since the Committee’s previous opinions (14 March 2007 and 16 July 2008).

The WHO recommends the following as first-line treatment for uncomplicated *Plasmodium falciparum* malaria (in 2011):

- In malaria-endemic areas, a combination containing a derivative of artemisinin:
  - artemether + lumefantrine (RIAMET)
  - dihydroartemisinin + piperaquine (EURARTESIM)
  - artesunate + amodiaquine (not available in France)
  - artesunate + mefloquine (not available in France)
  - artesunate + sulphadoxine-pyrimethamine (not available in France)
- In non-endemic regions (in cases of imported malaria), a combination of:
  - atovaquone + proguanil (MALARONE)
  - artemether + lumefantrine (RIAMET)
  - dihydroartemisinin + piperaquine (EURARTESIM)
  - oral quinine + doxycycline or clindamycin

The SPILF recommends the following as first-line treatment in France for uncomplicated *Plasmodium falciparum* malaria (in 2007):

- In adults:
  - 1st line: atovaquone + proguanil (MALARONE) or artemether + lumefantrine (RIAMET)
  - 2nd line: oral quinine or mefloquine (LARIAM)
  - 3rd line: halofantrine (HALFAN)
- In children and infants:
  - 1st line: mefloquine (LARIAM), atovaquone + proguanil (MALARONE) or artemether + lumefantrine (RIAMET)
  - 2nd line: halofantrine (HALFAN) or oral quinine
- In newborns:
  - 1st line: IV quinine, followed by switching to a single halofantrine (HALFAN) treatment
- Special cases: travellers returning from areas where there were high levels of resistance to mefloquine and halofantrine (the Amazon, including French Guiana, frontier regions between Thailand, Myanmar, Laos and Cambodia):
  - 1st line: atovaquone + proguanil (MALARONE), artemether + lumefantrine (RIAMET) or oral quinine + doxycycline or clindamycin

**Conclusion:**
RIAMET retains its role in the therapeutic strategy of uncomplicated *P. falciparum* malaria. Its availability to pharmacies aims to facilitate access to this medicine for some patients who are able to be treated in outpatients and avoid hospitalisations. The Committee issues a reminder that outpatient treatment for adults is restricted to patients with no hospitalisation criteria and that hospitalising young children is recommended in all cases. Any delay in malaria treatment may be fatal if *P. falciparum* is involved. Uncomplicated forms, with no digestive intolerance, are treated orally. Severe malaria is treated with intravenous quinine in ICU.

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8 Hospitalisation criteria: sign(s) of severity, area at risk, digestive intolerance preventing oral treatment, sociocultural or economic factors compromising the purchase of and/or good compliance with treatment, persons living alone, distance from a hospital centre, absence of readily available medicines in pharmacies, impossibility of follow-up, particularly on the 3rd and 7th days of treatment, platelets < 50,000/mm3, haemoglobin < 10 g/dl, creatinine > 150 µmol/l, parasitaemia > 2%.
In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

010.1 Actual benefit

- *P. falciparum* malaria is a serious disease on account of its potential deadliness. Strains of *Plasmodium falciparum* that are resistant to traditional treatments are becoming increasingly common. This parasitic disease is now covered by a WHO monitoring programme.1

- The artemether + lumefantrine (RIAMET) combination is intended as curative treatment for uncomplicated *P. falciparum* malaria.

- The efficacy/adverse effects ratio of this proprietary medicinal product is high so long as the contraindications (including congenital QTc-interval prolongation and certain heart disease antecedents), warnings and precautions for use are observed.

- This is a first-line therapy.

- There are treatment alternatives to this proprietary medicinal product.

Public health benefit:
The public health burden due to malaria is inconsiderable in France, given the limited number of cases (around 3500 cases each year in France).9,10,11,12,13,14,15 Improving the fight against malaria constitutes a major worldwide public health priority, with malaria already being targeted by a control programme run by the World Health Organisation. The fight against the disease vector remains the principal means of reducing malaria transmission at community level and the management of malaria cases (diagnosis and treatment) remains an essential component of any anti-malaria campaign. In France, the fight against malaria, which requires an integrated approach that comprises prevention and treatment with effective antimalarials, is not considered to be a public health priority established at national level. However, in French Guiana and Mayotte, where malaria is endemic, having access to artemisinin-based treatment combinations does constitute a response recognised by the WHO to the need to counter the risk that *P. falciparum* will become resistant to monotherapies, and to the spread of multidrug resistance to traditional antimalarials1.

Given the available data, a theoretical impact is expected on the reduction of morbidity and mortality linked to uncomplicated *Plasmodium falciparum* malaria. Given the small number of subjects potentially affected by treatment with the artemisinin-based combinations in France, no impact on a population level is expected.

Consequently, given the response which RIAMET could provide to the specific need for the affected populations in French Guiana and Mayotte, a minor public health benefit is expected for this proprietary medicinal product.

Taking account of these points, the Committee considers that the actual benefit of RIAMET is substantial in the indication and at the dosages in the Marketing Authorisation.

The Committee recommends inclusion of RIAMET 20 mg/120 mg, tablet on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication and at the dosages in the Marketing Authorisation.

**Proposed reimbursement rate: 65 %**

### 010.2 Improvement in actual benefit (IAB)

Given its efficacy in the treatment of uncomplicated malaria, particularly in the case of multidrug-resistant strains, and a lower risk of developing resistance with combinations containing artemisinin derivatives compared with traditional monotherapies, particularly in children and in malaria-endemic areas (mainly French Guiana and Mayotte), the proprietary medicinal product RIAMET, like the proprietary medicinal product EURARTESIM, provides a minor improvement in actual benefit (IAB IV) in the treatment of uncomplicated *Plasmodium falciparum* malaria.

### 010.3 Target population

The target population of RIAMET is made up of patients with uncomplicated *Plasmodium falciparum* malaria in adults, children and infants of 5 kg and above.

The epidemiology of malaria in France distinguishes between two situations: the imported cases and the native cases.

**Imported cases (metropolitan France and overseas departments and regions where malaria is not endemic):**

In metropolitan France, 1891 cases of imported malaria were reported in 2011 (including four deaths), 84% of which were due to *P. falciparum*.

Taking account of any under-reporting, the number of cases of imported malaria can be estimated at 3559 for 2011.

In Reunion Island, 47 cases of imported malaria were reported in 2012 (including one death), 94% of which were due to *P. falciparum*.

In Mayotte, 47 cases of imported malaria were reported in 2012 (no deaths), 91% of which were due to *P. falciparum*.

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Native cases (overseas departments and regions where malaria is endemic):
In French Guiana, 1048 cases of native malaria were reported between June 2012 and June 2013 (no deaths), 29% of which were due to *P. falciparum*.

In Mayotte, 25 cases of native malaria were reported in 2012 (no deaths), 91% of which were due to *P. falciparum*.

Conclusion:
The number of cases of *P. falciparum* malaria (metropolitan France and overseas departments and regions) would be around 3500 a year.

This estimation does not take into account potential underestimation in the overseas departments and regions.

In practice, the target population of RIAMET is smaller because of the absence of indication in the treatment of severe malaria, the absence of indication in children under 5 kg, and the potential contraindications, including congenital QTc-interval prolongation and certain heart disease antecedents. However, this target population is difficult to quantify.

In conclusion, on the basis of the most recent epidemiological data, the target population of RIAMET can be estimated to be up to 3500 patients a year.

### TRANSPARENCY COMMITTEE RECOMMENDATIONS

#### Packaging
The boxed packaging of 24 tablets is suitable for the prescribing conditions in adults and children of 12 years of age or over weighing 35kg or more.

It is not suitable for the prescribing conditions as regards dosage and treatment duration in children and infants of 5 kg to less than 35 kg requiring 6 to 18 tablets. However, this population is usually treated in hospital.

#### Other requests
The Committee regrets that there is no provision for pharmacies in metropolitan France of the alternatives MALARONE and LARIAM for the curative treatment of uncomplicated *Plasmodium falciparum* malaria.

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